Diagnostic Accuracy of the Aortic Dissection Detection Risk Score Plus D-Dimer for Acute Aortic Syndromes

The ADvISED Prospective Multicenter Study

Editorial, see p 270

BACKGROUND: Acute aortic syndromes (AASs) are rare and severe cardiovascular emergencies with unspecific symptoms. For AASs, both misdiagnosis and overtesting are key concerns, and standardized diagnostic strategies may help physicians to balance these risks. D-dimer (DD) is highly sensitive for AAS but is inadequate as a stand-alone test. Integration of pretest probability assessment with DD testing is feasible, but the safety and efficiency of such a diagnostic strategy are currently unknown.

METHODS: In a multicenter prospective observational study involving 6 hospitals in 4 countries from 2014 to 2016, consecutive outpatients were eligible if they had ≥1 of the following: chest/abdominal/back pain, syncope, perfusion deficit, and if AAS was in the differential diagnosis. The tool for pretest probability assessment was the aortic dissection detection risk score (ADD-RS, 0–3) per current guidelines. DD was considered negative (DD–) if <500 ng/mL. Final case adjudication was based on conclusive diagnostic imaging, autopsy, surgery, or 14-day follow-up. Outcomes were the failure rate and efficiency of a diagnostic strategy for ruling out AAS in patients with ADD-RS=0/DD– or ADD-RS ≤1/DD–.

RESULTS: A total of 1850 patients were analyzed. Of these, 438 patients (24%) had ADD-RS=0, 1071 patients (58%) had ADD-RS=1, and 341 patients (18%) had ADD-RS >1. Two hundred forty-one patients (13%) had AAS: 125 had type A aortic dissection, 53 had type B aortic dissection, 35 had intramural aortic hematoma, 18 had aortic rupture, and 10 had penetrating aortic ulcer. A positive DD test result had an overall sensitivity of 96.7% (95% confidence interval [CI], 93.6–98.6) and a specificity of 64% (95% CI, 61.6–66.4) for the diagnosis of AAS; 8 patients with AAS had DD–. In 294 patients with ADD-RS=0/DD–, 1 case of AAS was observed. This yielded a failure rate of 0.3% (95% CI, 0.1–1.9) and an efficiency of 15.9% (95% CI, 14.3–17.6) for the ADD-RS=0/DD– strategy. In 924 patients with ADD-RS ≤1/DD–, 3 cases of AAS were observed. This yielded a failure rate of 0.3% (95% CI, 0.1–1) and an efficiency of 49.9% (95% CI, 47.7–52.2) for the ADD-RS ≤1/DD– strategy.

CONCLUSIONS: Integration of ADD-RS (either ADD-RS=0 or ADD-RS ≤1) with DD may be considered to standardize diagnostic rule out of AAS.

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Clinical Perspective

What Is New?

- The ADvISED international multicenter study (Aortic Dissection Detection Risk Score Plus D-Dimer in Suspected Acute Aortic Dissection) prospectively assessed the diagnostic performance of standardized strategies integrating pretest probability assessment and D-dimer in 1850 patients from the emergency department.
- The aortic dissection detection risk score (ADD-RS), a bedside clinical tool for standardized pretest probability assessment, effectively stratified the risk of acute aortic syndrome (AAS).
- In patients with ADD-RS >1 and D-dimer <500 ng/mL, the rate of AAS was significant (1 in 22 cases).
- Rule out strategies for AAS integrating ADD-RS=0 plus D-dimer <500 ng/mL or ADD-RS ≤1 plus D-dimer <500 ng/mL were found to miss ≈1 in 300 cases of AAS.

What Are the Clinical Implications?

- Integration of ADD-RS with D-dimer may help to standardize diagnostic decisions on advanced imaging for suspected AAS, balancing the risks of misdiagnosis and overtesting.
- Patients at high probability of AAS (ie, ADD-RS >1) should proceed to computed tomography angiography or other conclusive imaging regardless of D-dimer levels.
- ADD-RS=0 plus D-dimer <500 ng/mL and ADD-RS ≤1 plus D-dimer <500 ng/mL are possible rule out diagnostic strategies for AAS.
- The ADD-RS ≤1 plus D-dimer <500 ng/mL strategy may avoid up to 1 in 2 computed tomography angiography examinations in patients with suspected AAS.

Acute aortic syndromes (AASs), which include aortic dissection, intramural aortic hematoma, penetrating aortic ulcer, and aortic rupture, are life-threatening cardiovascular emergencies affecting 3 to 6 per 100 000 individuals a year.[1,2] AASs constitute a diagnostic challenge because their clinical presentation is highly unspecific.[3] Indeed, although key symptoms of AASs such as chest pain account for millions of emergency department (ED) visits worldwide every year, AAS is the responsible cause in only a small minority of patients.[4] Accordingly, the misdiagnosis rate of AAS is 14% to 39% and represents a substantial concern.[5–7]

Chest and abdomen computed tomography angiography (CTA) can accurately diagnose AAS but exposes patients to risks of radiation and contrast-induced anaphylaxis and nephropathy.[3,8,9] Differences across centers notwithstanding, as few as 2.7% of CTA examinations performed for suspected AAS were positive in an ED-based series.[10] In addition, other advanced imaging methods such as transesophageal echocardiography (TEE) and aortic magnetic resonance angiography (MRA) are stress limited, potentially harmful, and costly, demanding careful patient selection. Therefore, algorithms helping physicians to reduce both misdiagnosis and overtesting for AAS are highly needed.

The aortic dissection detection (ADD) risk score (ADD-RS) is a tool allowing standardized assessment of the pretest probability AAS.[11] On the basis of the ADD-RS, patients can be classified in 3 (ADD-RS=0, ADD-RS=1, ADD-RS >1) or 2 (ADD-RS ≤1, ADD-RS >1) categories. This classification is adopted by international guidelines and inspires the proposed diagnostic algorithms for AAS.[12,13]

D-dimer (DD) is a well-established rule-out biomarker for pulmonary embolism.[14,15] Several studies have shown that DD is also highly sensitive for AAS.[16,17] However, a negative DD test result per se is insufficient for AAS rule out in any patient.[18] Because only very few cases of AAS are predicted to occur in patients at lower pretest probability also testing negative for DD, combined use of ADD-RS and DD testing could allow safe rule out of AAS without conclusive imaging.[13,15,17,19–21] This approach has never been evaluated prospectively. We have performed a prospective multicenter study assessing the accuracy and efficiency of a diagnostic strategy integrating ADD-RS with DD testing.

METHODS

The data, analytical methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure by contacting the corresponding author (F.M.). For expanded methods, see the online-only Data Supplement.

Study Design and Setting

This was a multicenter, multinational, prospective, diagnostic accuracy observational study involving 6 hospitals and 150 physicians in 4 countries. The ethics committees of the participating centers approved the study. Written informed consent of participants was obtained for inclusion. The study was registered on http://www.clinicaltrials.gov (NCT02086136).

Patient Selection

From 2014 to 2016, consecutive outpatients >18 years presenting to the ED were eligible if they experienced ≥1 of the following symptoms within ≤14 days: chest pain, abdominal pain, back pain, syncope, or signs or symptoms of perfusion deficit. Patients were included only if AAS was considered in the differential diagnosis by the attending physician, which defined a provider-determined need for rule out of AAS. Subjects were enrolled 24 hours a day, 7 days a week. Exclusion criteria were primary trauma and unwillingness or inadequacy to participate in the study.

Index Visit

Patients were evaluated by ≥1 physicians. After eligibility assessment, a case report form was completed, and a DD test was ordered. Subsequent diagnostic and clinical decisions were based on clinical judgment by physicians who were not blinded to the items for pretest probability assessment and to the DD test result.

Pretest Probability Assessment

The tool used to assess the pretest probability of AAS was the ADD-RS, based on 12 risk markers classified in 3 categories (Table I in the online-only Data Supplement).[11–13,21,22] The ADD-RS of each patient was automatically calculated as the number of categories (0–3) in which at least 1 risk marker was present.[12,13]

D-Dimer

Patients were subjected to venous sampling during the index visit. The samples were immediately sent to the local laboratory for automated DD assay. A DD test result was defined negative if <500 ng/mL fibrinogen equivalent units.[16,17]

Diagnostic Workup and Follow-Up

The following advanced imaging methods were considered conclusive for the diagnosis of AAS: CTA, TEE, and MRA. Patients not subjected to these tests and without surgical or autopsy data confirming or excluding AAS entered a 14-day clinical follow-up for case adjudication. For this purpose, patients or family members were interviewed by telephone with a structured questionnaire or underwent an outpatient visit after 14 days from ED discharge. The following events were queried: diagnosis of AAS or any aortic disease, subsequent ED visit, hospital admission, and death. Patients dismissed from the ED were instructed to return to the ED in case of new, worsening, or recurrent symptoms. Hospital charts and dismissal documents of all enrolled patients were acquired and reviewed for case adjudication.

Case Definition and Adjudication

The definition of AAS included Stanford type A or B aortic dissection, aortic intramural hematoma, penetrating aortic ulcer, and aortic rupture. Case adjudication was performed by 2 expert physicians who independently reviewed the diagnostic data obtained during the index ED visit and during the 14-day follow-up period while blinded to the ADD-RS and to the DD test result. A case of AAS was predefined by evidence of AAS on CTA, TEE, MRA, surgery, or autopsy. For deaths occurring in patients without conclusive imaging, surgery, or autopsy, adjudication was clinical. Case adjudication was dichotomic: AAS present or absent. In patients without AAS, an alternative diagnosis was indicated.

Outcomes

The primary outcome was the failure rate of 2 diagnostic strategies ruling out AAS, 1 in patients with ADD-RS=0 and a negative DD test result (ADD-RS=0/DD–) and 1 in patients with ADD-RS ≤1 and a negative DD test result (ADD-RS ≤1/DD–). The failure rate was computed as the number of adjudicated AAS diagnoses divided by the number of patients with negative DD within a risk category. The secondary outcome was the efficiency in ruling out AAS of the 2 diagnostic strategies. This was computed as the number of patients with negative DD within a risk category divided by the number of enrolled patients.

Statistical Analysis

General characteristics were assessed with mean and SD, median and interquartile range, and proportions and 95% confidence intervals (CIs). Univariate logistic regression models were used to assess the association (odds ratio) between AAS and selected categorical and continuous independent

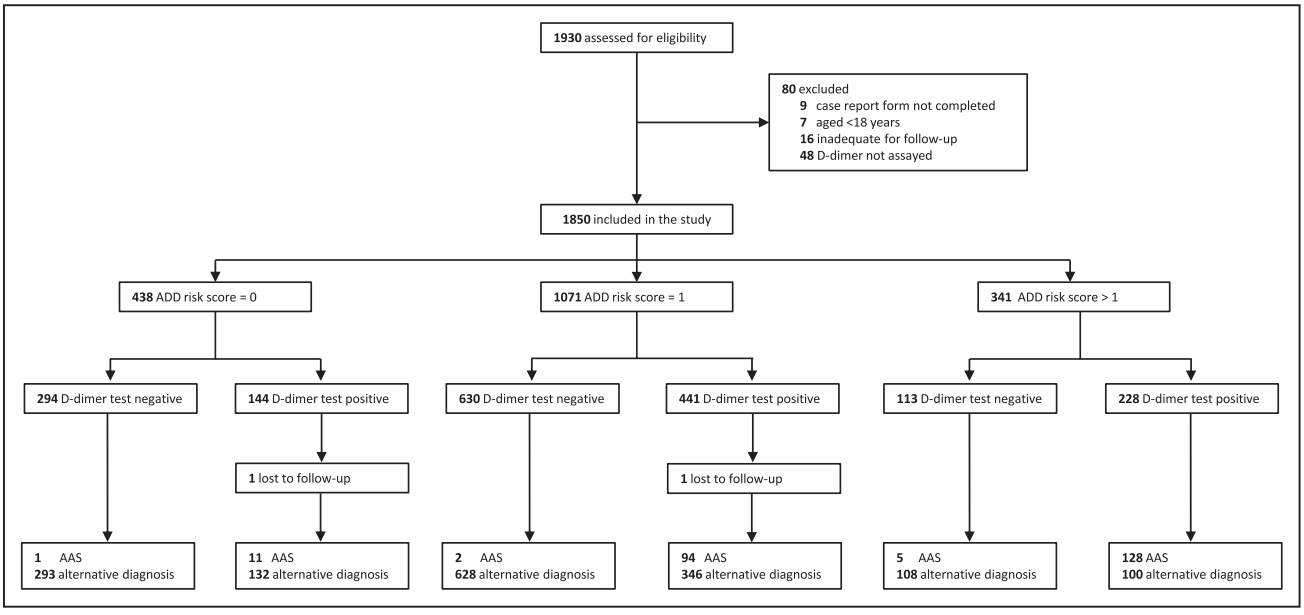

Figure 1. Study flow chart.
AAS indicates acute aortic syndrome; and ADD, aortic dissection detection.

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variables. Statistical differences were compared with the 2-tailed Student *t* test for independent samples or χ^2 test. *P* values were considered significant if <0.05.

The present study was powered to test the null hypothesis that the failure rate of the indicated diagnostic rule out strategies exceeds 2%. This was based on previous estimates that the threshold clinical probability of AAS above which the benefits of testing outweigh its risks is 3% for CTA.[23] Using a type I error of 0.05 (1 sided) and type II error of 0.2, we estimated that at least 1767 patients needed to be included.

RESULTS

Patients

Prospective data were collected for 1930 patients (Figure 1). Because 80 patients had exclusion criteria, 1850 patients were enrolled in the study (Table 1). The prevalence of the ADD-RS risk markers is presented in Table II in the online-only Data Supplement. Four hundred thirty-eight patients (23.7%) had ADD-RS=0 and 1071 (57.9%) had ADD-RS=1; 1509 patients (81.6%) were classified at nonhigh risk of AAS (ADD-RS ≤1), and 341 patients (18.4%) had ADD-RS >1.

Overall, the DD test was positive (≥500 ng/mL) in 813 patients (43.9%). The DD test was positive in 144 patients (32.9%) with ADD-RS=0 and in 441 patients (41.2%) with ADD-RS=1. Hence, the DD test was positive in 585 patients (38.8%) with ADD-RS ≤1. The DD test was positive in 228 patients (66.9%) with ADD-RS >1 (*P*<0.001 versus ADD-RS ≤1).

Diagnostic Workup and Case Adjudication

For 865 study patients (46.8%), conclusive diagnostic data were obtained by CTA, TEE, MRA, surgery, or autopsy (Figure 2). The ADD-RS classification of these patients was as follows: ADD-RS=0 in 169 patients (38.9%), ADD-RS=1 in 439 (41%), and ADD-RS >1 in 257 (75.4%). Two patients were lost to follow-up, and 3 patients died without advanced imaging or surgery (all had positive DD; Tables III and IV in the online-only Data Supplement).

AAS was adjudicated in 241 patients (13%; Table V in the online-only Data Supplement): type A aortic dis-

Table 1. Demographic and Clinical Characteristics of the Study Patients

Characteristic	All Patients* (n=1850)	Acute Aortic Syndrome (n=241)	Alternative Diagnosis (n=1607)	Odds Ratio (95% CI)	*P* Value
Demographic data					
Age, y	62 (50–74)	67 (58–78)	61 (49–73)	1.51 (1.3–1.75)	<0.001
Female sex, n (%)	698 (37.7)	74 (30.7)	624 (38.8)	0.7 (0.52–0.93)	0.015
Medical history, n (%)					
Hypertension	1024 (55.4)	172 (72.3)	850 (52.9)	2.32 (1.72–3.13)	<0.001
Diabetes mellitus	251 (13.6)	19 (8)	231 (14.4)	0.52 (0.32–0.84)	0.007
Smoker	636 (34.5)	64 (26.9)	572 (35.6)	0.66 (0.49–0.9)	0.008
Illicit drug use	12 (0.8)	3 (1.3)	9 (0.7)	1.79 (0.48–6.66)	0.379
Coronary artery disease	337 (18.2)	20 (8.4)	316 (19.7)	0.37 (0.23–0.60)	<0.001
Abdominal aortic aneurysm	103 (5.6)	26 (10.9)	77 (4.8)	2.44 (1.53–3.89)	<0.001
Clinical presentation					
Time from onset, h	7.5 (2–30)	3 (2–14.5)	8 (3–48)	0.8 (0.67–0.95)	0.006
Anterior chest pain, n (%)	1403 (75.8)	159 (66)	1244 (77.4)	0.57 (0.42–0.76)	<0.001
Posterior chest pain, n (%)	506 (27.4)	104 (43.2)	401 (25)	2.28 (1.73–3.02)	<0.001
Abdominal pain, n (%)	287 (15.5)	60 (24.9)	226 (14.1)	2.03 (1.46–2.8)	<0.001
Lumbar pain, n (%)	123 (6.6)	29 (12)	93 (5.8)	2.23 (1.43–3.46)	<0.001
Any pain, n (%)	1711 (92.5)	224 (92.9)	1485 (92.4)	1.08 (0.64–1.83)	0.77
Syncope, n (%)	211 (11.4)	44 (18.3)	167 (10.4)	1.93 (1.34–2.77)	<0.001
Perfusion deficit, n (%)	147 (7.9)	53 (22)	94 (5.8)	4.54 (3.14–6.56)	<0.001
Clinical features					
Systolic blood pressure, mm Hg	140±26	131±39	139±28	0.69 (0.59–0.79)	0.001
Diastolic blood pressure, mm Hg	81±14	76±22	80±16	0.76 (0.66–0.87)	0.004
Pulse, bpm	78±18	78±23	78±18	0.98 (0.85–1.13)	0.838

Categorical variables are presented as number (percent); age and time from onset are presented as median and 25th through 75th interquartile range; clinical features as presented as mean±SD. For continuous variables, odds ratios are referred to 1 SD.
CI indicates confidence interval.
*Includes 2 patients who were further lost to follow-up for whom final case adjudication was not possible.

section in 125 (6.8%), type B dissection in 53 (2.9%), intramural aortic hematoma in 35 (1.9%), aortic rupture in 18 (1%), and penetrating aortic ulcer in 10 (0.5%). In 1607 patients (87%), AAS was adjudicated as absent. The alternative diagnoses were muscle-skeletal chest pain (485 patients, 26.2%), acute coronary syndrome (244, 13.2%), gastrointestinal disease (191, 10.3%), syncope (78, 4.2%), pleuritis or pneumonia (57, 3.1%), pericarditis (54, 2.9%), uncomplicated aortic aneurysm (53, 2.9%), pulmonary embolism (30, 1.6%), stroke (15, 0.8%), limb ischemia (2, 0.1%), and other diagnoses (398, 21.5%).

ADD-RS Classification

The classification of patients with AAS was ADD-RS=0 in 12 patients (5%), ADD-RS=1 in 96 (39.8%), and ADD-RS >1 in 133 (55.2%). The prevalence of AAS was 2.7% in patients with ADD-RS=0, 9% in patients with ADD-RS=1, and 39% in patients with ADD-RS >1.

Presence of ADD-RS ≥1 had a sensitivity of 95% (95% CI, 91.5–97.4) and a specificity of 26.4% (95% CI, 24.3–28.7) for the diagnosis of AAS. The positive predictive value of ADD-RS ≥1 was 16.2% (95% CI, 14.3–18.3), the positive likelihood ratio was 1.29 (95% CI, 1.24–1.35), the negative predictive value was 97.3% (95% CI, 95.3–98.6), and the negative likelihood ratio was 0.19 (95% CI, 0.11–0.33).

D-Dimer

The median levels of DD were 5810 ng/mL (95% CI, 596–50983) in AAS and 370 ng/mL (95% CI, 98–5560) in alternative diagnoses (P<0.001; Figure I in the online-

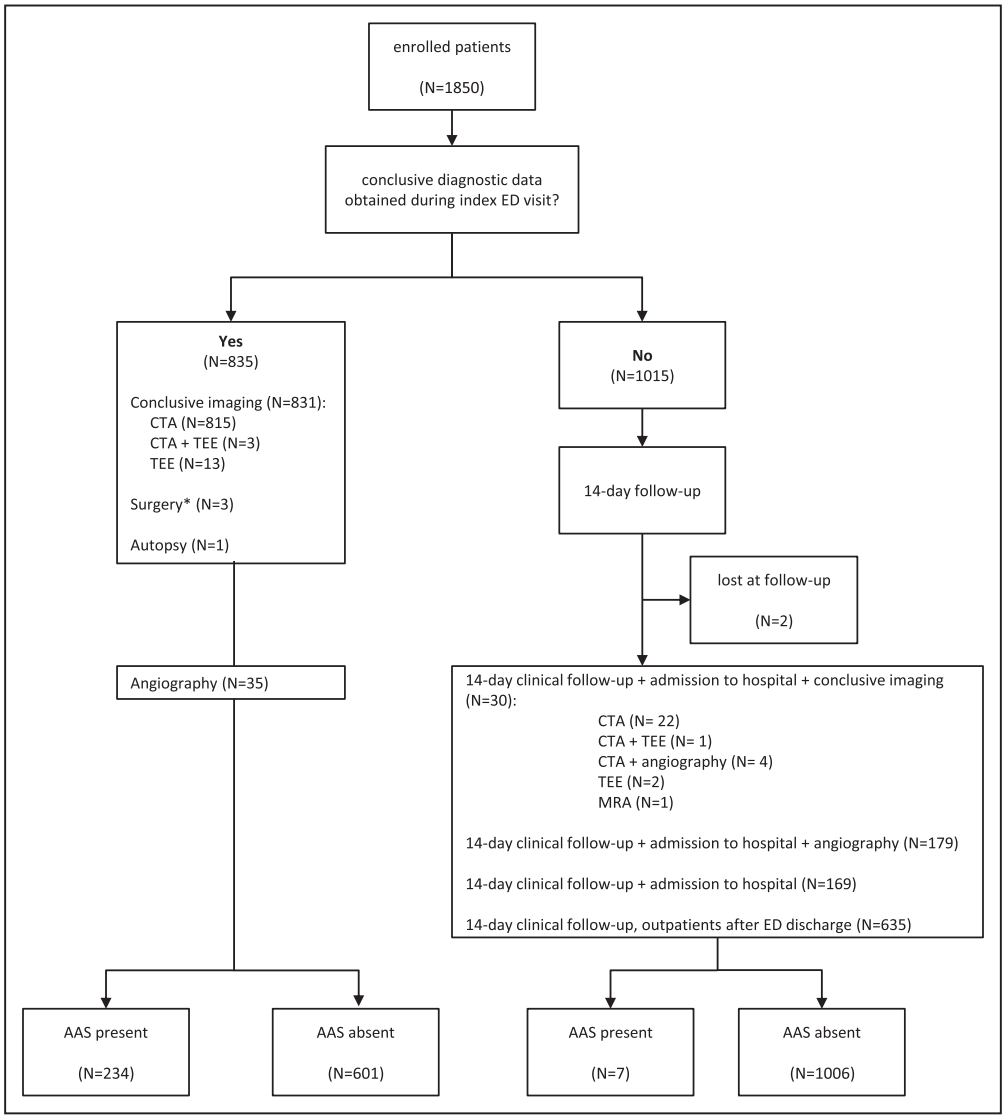

Figure 2. Flow chart summarizing diagnostic workup.
AAS indicates acute aortic syndrome; CTA, computed tomography angiography; ED, emergency department; MRA, magnetic resonance angiography; and TEE, transesophageal echocardiography. *Without previous conclusive imaging.

only Data Supplement). A positive DD test (≥500 ng/mL) had an overall sensitivity of 96.7% (95% CI, 93.6–98.6) and a specificity of 64% (95% CI, 61.6–66.4) for the diagnosis of AAS. The positive predictive value was 28.7% (95% CI, 25.6–32); the positive likelihood ratio was 2.69 (95% CI, 2.51–2.88); the negative predictive value was 99.2% (95% CI, 98.5–99.7); and the negative likelihood ratio was 0.05 (95% CI, 0.03–0.1). Eight patients with AAS tested negative for DD (Table 2).

Integration of ADD-RS With DD

We estimated the performance of 2 rule-out strategies for AAS: ADD-RS=0/DD– and ADD-RS ≤1/DD– (Table 3 and Table VI in the online-only Data Supplement). In patients with ADD-RS=0, DD was negative in 294 individuals. In this low-risk subgroup, 1 case of AAS was observed. This yielded for the ADD-RS=0/DD– strategy a failure rate of 0.3% (95% CI, 0.1–1.9), corresponding to 1 missed case in 294 patients. The efficiency in ruling out AAS was 15.9% (95% CI, 14.3–17.6), corresponding to 1 in 6 patients. In patients with ADD-RS ≤1, DD was negative in 924 individuals (50%). In this non–high-risk subgroup, 3 cases of AAS were observed. This yielded for the ADD-RS ≤1/DD– strategy a failure rate of 0.3% (95% CI, 0.1–1), corresponding to 1 missed case in 312 patients. The efficiency in ruling out AAS was 49.9% (95% CI, 47.7–52.2), corresponding to 1 in 2 patients.

In patients with ADD-RS >1, DD was negative in 113 individuals (33.1%), and 5 cases of AAS were observed. This yielded a failure rate of 4.4% (95% CI, 1.9–9.9), corresponding to 1 missed case in 22 patients.

DISCUSSION

The present study is the first to obtain direct prospective evidence that in patients without risk factors for AAS (ie, ADD-RS=0) testing negative for DD, the rate of AAS diagnosis was ≈1 missed case in 300 patients. Application of this rule may potentially spare ≈3 in 5 conclusive imaging examinations in this patient category and 1 in 6 conclusive imaging examinations in all patients with suspected AAS. Another key finding is that in patients presenting with a high pretest probability of AAS (ie, ADD-RS >1), the rate of AAS was significant (4%) even if the DD tested negative, thus confirming that this approach is not suitable in this patient group. Finally, in the large group of patients at nonhigh pretest probability of AAS (ie, ADD-RS≤1) testing negative for DD, the rate of AAS diagnosis was also ≈1 missed case in 300 patients. Application of this rule may potentially spare ≈3 in 5 conclusive imaging examinations in this patient category and 1 in 2 conclusive imaging examinations in all patients with suspected AAS. It was previously hypothesized that only the ADD-RS=0/DD– strategy should be considered for AAS rule out.[17] In the present study, in which the prevalence of AAS in patients with ADD-RS=1 was only 9%, the failure rate was low for both the ADD-RS=0/DD– and ADD-RS ≤1/DD– strategies. The likely cause lies in the systematic application of the ADD-RS, which led to better identification of risk factors for AAS.

The acceptable failure rate of a rule out strategy for AAS is not yet established. Similar algorithms have been considered safe for pulmonary embolism if the upper limit of the 95% CI around the failure was <3%.[14,24,25]

Table 2. Clinical Details of Study Patients With an AAS Testing Negative for DD

Patient No.	Clinical Description	Time From Symptom Onset	ADD Risk Factors	ADD-RS	Chest X-Ray	AAS Type
1	78-y-old woman; history of hypertension, diabetes mellitus, smoking; posterior chest pain, high blood pressure at visit	7 d	None	0	Enlarged mediastinum	B-AD
2	72-y-old man; history of hypertension, CAD; anterior chest pain, syncope	2 h	Sudden, severe, ripping pain	1	Normal mediastinum	A-AD
3	34-y-old man; silent history; anterior and posterior chest pain, syncope	2 h	Sudden, severe, ripping pain	1	Enlarged mediastinum	A-AD
4	40-y-old man; silent history; anterior chest pain	1 h	Sudden pain; family history of AAS	2	Normal mediastinum	A-AD
5	75-y-old man; history of hypertension, diabetes mellitus, CAD; anterior and posterior chest pain	24 h	Sudden, severe, ripping pain; pulse deficit	2	Normal mediastinum	IMH
6	59-y-old man; history of hypertension; anterior and posterior chest pain	2 h	Known TAA; sudden, severe pain	2	Not done	IMH
7	54-y-old man; history of AAS; anterior and posterior chest pain	23 h	Sudden pain; pulse deficit	2	Normal mediastinum	Spontaneous aortic rupture
8	46-y-old man; history of smoking; anterior chest and abdominal pain	7 d	Sudden, severe pain; diastolic murmur	2	Not done	A-AD

A-AD indicates Stanford type A aortic dissection; AAS, acute aortic syndrome; ADD, aortic dissection detection; ADD-RS, aortic dissection detection risk score; B-AD, Stanford type B aortic dissection; CAD, coronary artery disease; DD, D-dimer; IMH, intramural aortic hematoma; and TAA, thoracic aortic aneurysm.

Table 3. Diagnostic Variables of the ADD-RS Integrated With DD Testing for Diagnosis or Rule Out of AAS in 1848 Included Patients

Diagnostic Variable	Diagnostic Strategy (95% CI)	
	ADD-RS=0 Plus DD <500 ng/mL	ADD-RS ≤1 Plus DD <500 ng/mL
Sensitivity, %	99.6 (97.7–100)	98.8 (96.4–99.7)
Specificity, %	18.2 (16.4–20.2)	57.3 (54.9–59.7)
PPV, %	15.4 (13.7–17.3)	25.8 (23–28.7)
LR+	1.22 (1.19–1.25)	2.31 (2.18–2.45)
NPV, %	99.7 (98.1–100)	99.7 (99.1–99.9)
LR–	0.02 (0.003–0.16)	0.02 (0.01–0.07)

AAS indicates acute aortic syndrome; ADD-RS, aortic dissection detection risk score; CI, confidence interval; DD, D-dimer; LR, likelihood ratio; NPV, negative predictive value; and PPV, positive predictive value.

In a previous study, the threshold clinical probability of AAS above which the benefits of testing outweigh its risks was 3% for CTA.[23] In the present study, the upper limit of the 95% CI around the failure rate was 1.9% for the ADD-RS=0/DD– strategy and 1% for the ADD-RS ≤1/DD– strategy. Empirical judgment on these rule-out strategies needs to strongly consider the current disappointing data from clinical practice showing that the misdiagnosis rate of AAS reaches 40% and that only 2.7% of CTA examinations requested for possible AAS turn out positive.[5–7,10]

The present study has limitations. First, although the symptoms triggering screening were prespecified, the entry criterion was a provider-determined need for rule out of AAS, which is hard to standardize. In this respect, results from urban teaching hospitals may not be generalized. In clinical practice, the actual failure and efficiency of the diagnostic strategies ultimately depend on the number and type of patients receiving testing, and inappropriate DD testing may paradoxically increase the number of patients undergoing CTA. Second, attending physicians were not blinded to ADD-RS data and to DD test results, for clinical and ethical reasons, as in the IRAD-Bio study (International Registry of Acute Aortic Dissection Substudy on Biomarkers).[13,26] This likely affected their decision to perform conclusive imaging.

Third, about half of study patients were not subjected to conclusive diagnosis with CTA, TEE, MRA, surgery, or autopsy, and their case adjudication was based on 14-day clinical follow-up data only. This follow-up approach was tailored on the assumption that individuals with undiagnosed AAS would experience major clinical events leading to repeated medical evaluation and conclusive diagnosis within 14 days from the ED visit, but this has not been validated. Among patients with a negative DD in follow-up, none were lost to follow-up, none died without a clear cause, and 7 cases of AAS were identified during the specified follow-up period, which strengthen our findings. Clinical follow-up data were also supported in 37% of the patients by hospitalization data after the index visit. Nonetheless, we cannot exclude with certainty that in 731 study patients with ADD-RS ≤1/DD– and a negative 14-day follow-up, few cases of AAS with mild or atypical manifestations might have been missed. Such a clinical scenario is hardly compatible with type A dissections and may essentially derive from intramural hematomas, ulcers, or short type B dissections.

A flowchart summarizing the proposed diagnostic approach to suspected AAS in the ED is presented in Figure 3. Expert evaluation and debate in the medical community are needed to define whether these strategies meet safety and efficiency criteria for their recommendation in clinical practice.

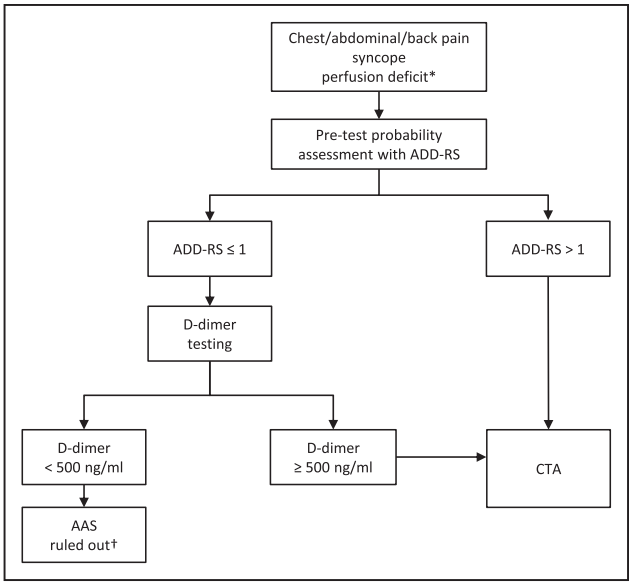

Figure 3. Proposed diagnostic algorithm based on pre-test probability assessment and D-dimer.
AAS indicates acute aortic syndrome; ADD-RS, aortic dissection detection risk score; and CTA, computed tomography angiography. *AAS in differential diagnosis. †Caution in patients with early presentation (≤2 hours) or long-lasting symptoms (≥1 week; see Table 2).

APPENDIX

The ADvISED Study (Aortic Dissection Detection Risk Score Plus D-Dimer in Suspected Acute Aortic Dissection) Investigators

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DISCLOSURES

None.

AFFILIATIONS

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FOOTNOTES

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